



## Meta-Analysis

### Type of Alcoholic Beverage and Risk of Head and Neck Cancer—A Pooled Analysis Within the INHANCE Consortium

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The authors pooled data from 15 case-control studies of head and neck cancer (9,107 cases, 14,219 controls) to investigate the independent associations with consumption of beer, wine, and liquor. In particular, they calculated associations with different measures of beverage consumption separately for subjects who drank beer only (858 cases, 986 controls), for liquor-only drinkers (499 cases, 527 controls), and for wine-only drinkers (1,021 cases, 2,460 controls), with alcohol never drinkers (1,124 cases, 3,487 controls) used as a common reference group. The authors observed similar associations with ethanol-standardized consumption frequency for beer-only drinkers (odds ratios (ORs) = 1.6, 1.9, 2.2, and 5.4 for  $\leq 5$ , 6–15, 16–30, and  $>30$  drinks per week, respectively;  $P_{\text{trend}} < 0.0001$ ) and liquor-only drinkers (ORs = 1.6, 1.5, 2.3, and 3.6;  $P < 0.0001$ ). Among wine-only drinkers, the odds ratios for moderate levels of consumption frequency approached the null, whereas those for higher consumption levels were comparable to those of drinkers of other beverage types (ORs = 1.1, 1.2, 1.9, and 6.3;  $P < 0.0001$ ). Study findings suggest that the relative risks of head and neck cancer for beer and liquor are comparable. The authors observed weaker associations with moderate wine consumption, although they cannot rule out confounding from diet and other lifestyle factors as an explanation for this finding. Given the presence of heterogeneity in study-specific results, their findings should be interpreted with caution.

alcohol drinking; alcoholic beverages; beer; case-control studies; head and neck neoplasms; meta-analysis; wine

Abbreviations: CI, confidence interval; HNC, head and neck cancer; INHANCE, International Head and Neck Cancer Epidemiology; OR, odds ratio.

Alcohol consumption is a major risk factor for head and neck cancer (HNC), that is, cancers of the oral cavity, pharynx, and larynx (1, 2). Although the causal mechanism is not fully understood, ethanol may influence cancer risk directly through topical carcinogenic effects and/or indirectly by enhancing the effects of other carcinogens (e.g., tobacco) (1–3). There is speculation that other ingredients of alcoholic beverages besides ethanol may additionally influence

cancer risk. Asbestos filtration products, tannins, *N*-nitroso compounds, urethane, and other possible carcinogens have been found in some alcoholic beverages (1, 3). Conversely, antioxidants, such as resveratrol, found in red wine may be anticarcinogenic (4).

In light of this uncertainty surrounding the mechanisms underlying alcohol-induced carcinogenesis, there has been interest as to whether different alcoholic beverages are

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differentially associated with HNC risk. There are several reports of differences in relative risk among beer, wine, and liquor consumption (Web Table 1). (This information is described in the first of 6 supplementary tables; each is referred to as "Web table" in the text and is posted on the *Journal's* website (<http://aje.oxfordjournals.org/>).) However, the observed differences in risk are inconsistent across studies (5–17). A common limitation of these studies is the inability to adequately isolate the effects of beer, wine, and liquor consumption, given their intercorrelated patterns of consumption in many populations. One method of addressing this issue is to identify drinkers of only beer, wine, or liquor and to estimate their respective associations with HNC risk relative to never drinkers. However, limitations in sample size among individual studies have prevented the use of this analytical approach across all 3 beverage types.

Larger studies are needed to adequately investigate the effects of different alcoholic beverages; with this in mind, we conducted a pooled analysis of studies participating in the International Head and Neck Cancer Epidemiology (INHANCE) Consortium to investigate the independent associations with HNC risk for consumption of beer, wine, and liquor. In particular, we estimated these associations among persons who consumed 1 beverage type exclusively (referred to hereafter as "pure drinkers").

## MATERIALS AND METHODS

A detailed description of the INHANCE Consortium has been previously published (18). For the purposes of this study, HNC cases were restricted to invasive tumors of the oral cavity, oropharynx, hypopharynx, oral cavity or pharynx not otherwise specified, larynx, and HNC unspecified (18). Cancers of the salivary gland (*International Classification of Diseases for Oncology*, Second Edition, codes C07–C08) were excluded from our analysis because of the different etiologic pattern from that of other HNCs. The INHANCE pooled data set (version 1.1) used for this analysis included 15 individual case-control studies, comprising 10,301 HNC cases and 15,329 controls (19–32). Individuals with missing data on age, sex, or race/ethnicity were excluded (23 cases, 102 controls), as were subjects with missing or conflicting information regarding drinking status (620 cases, 390 controls). Finally, participants from the India and Sudan centers of the International Agency for Research on Cancer Multicenter Study (32) were excluded (551 cases, 618 controls) because of the extremely low prevalence of alcohol consumption in these populations. After these exclusions, the data set for this analysis included 9,107 HNC cases and 14,219 controls.

Characteristics of the studies included in the pooled data are shown in Table 1. Most were hospital based, and all included controls frequency matched to cases on age, sex, and additional factors. Study interviews were conducted face-to-face, except in Iowa where subjects completed self-administered questionnaires. Written, informed consent was obtained from all study subjects, and the investigations were approved by institutional review boards at each of the institutes involved. All study questionnaires were reviewed

to assess the comparability of the data and wording of interview questions. The questionnaires were conceptually similar across studies; subjects were asked if they were alcohol drinkers (definitions by study are included in the Appendix) and then asked subsequent questions on frequency of drinking, duration of drinking, and different types of alcoholic beverages consumed. Data from individual studies were received by the pooling center with personal identifiers removed. Each data item was checked for illogical or missing values. Queries were sent to investigators, and inconsistencies were resolved.

To facilitate comparisons of consumption frequency across alcoholic beverage types and to adjust for differences between studies in specified beverage volumes, we standardized the calculated average beverage-specific weekly number of drinks on the basis of ethanol volume. We calculated this measure for each alcoholic beverage type by converting the beverage volume specified in the questionnaire to milliliters, multiplying this by the average number of drinks per week of that beverage, applying estimates of the beverage-specific volume percentage of pure ethanol (5% for beer, 12% for wine, 40% for liquor) (1), and dividing the weekly consumption of pure ethanol by the average per-drink volume of pure ethanol across alcoholic beverage types for the 15 studies (15.6 mL). The standardized estimates of beverage consumption frequency can thus be assumed to have, on average, identical volumes of ethanol per drink.

The cutpoints for categorizing the average weekly number of ethanol-standardized drinks for a beverage (never drinker,  $\leq 5$ , 6–15, 16–30,  $>30$  drinks per week) were selected to maximize the number of categories of consumption level while minimizing the occurrence of sparse data within the upper categories for some studies. This latter issue arose because of considerable variation across populations in the popularity of different beverages, as is summarized in Table 1. Participants in European studies consumed larger quantities of wine than did subjects from North and Latin America. Less extreme differences were observed for liquor consumption (generally higher in North and Latin American studies), while beer consumption was fairly uniform across studies. For each alcoholic beverage, we also calculated the duration (never drinker,  $\leq 10$ , 11–20, 21–40,  $>40$  years) of consumption reported by subjects and the lifetime cumulative number of standardized drinks consumed (never drinker,  $\leq 10$ , 11–20, 21–40, 41–80,  $>80$  drink-years; calculation previously described (18)).

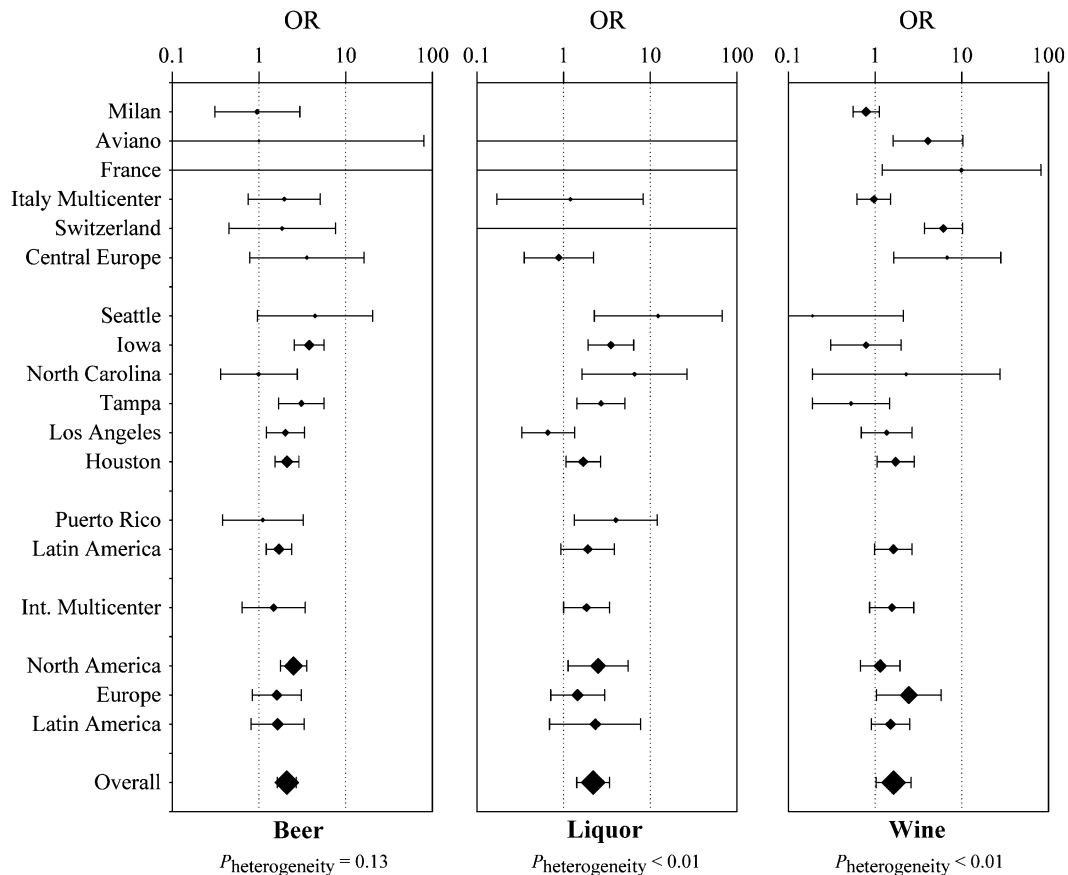
From the data on alcohol consumption, we were able to identify mutually exclusive subgroups across studies: never drinkers (1,124 cases, 3,487 controls), drinkers of beer only (858 cases, 986 controls), drinkers of liquor only (499 cases, 527 controls), drinkers of wine only (1,021 cases, 2,460 controls), and drinkers of multiple beverage types (5,605 cases, 6,759 controls). Our analyses focused on investigations of alcoholic beverage consumption (ethanol-standardized consumption frequency, duration of consumption, lifetime cumulative consumption) among each of the groups of pure drinkers, with never drinkers as a common reference group. However, we also examined associations with beverage-specific, ethanol-standardized consumption frequency

**Table 1.** Summary of Individual Studies in the INHANCE Consortium Pooled Analysis of Alcoholic Beverages

Reference <sup>a</sup>	Study Location	Recruitment Period	Age Eligibility, years	Cases			Controls <sup>b</sup>		Median Drinks Per Week Among Drinkers		
				Sites	Source	Participation Rate, %	Source	Participation Rate, %	Beer	Liquor	Wine
				Europe							
19	Milan, Italy	1984–1989	<80	Oral cavity, pharynx, larynx	Hospital	95 <sup>c</sup>	Hospital—unhealthy	95 <sup>c</sup>	0	0	21
20	Aviano, Italy	1984–1989	>18	Oral cavity, pharynx, larynx	Hospital	>95 <sup>c</sup>	Hospital—unhealthy	95 <sup>c</sup>	0	0	28
21	France	1987–1992	N/R	Oral cavity, pharynx, larynx	Hospital	95 <sup>c</sup>	Hospital—unhealthy	95 <sup>c</sup>	7	0	28
22	Aviano, Milan, and Latina, Italy	1990–1999	18–80	Oral cavity, pharynx, larynx	Hospital	>95	Hospital—unhealthy	95	1	1	19
23	Switzerland	1991–1997	<80	Oral cavity, pharynx, larynx	Hospital	95	Hospital—unhealthy	95	0	0	12
24	Central Europe	1998–2003	≥15	Oral cavity, pharynx, larynx	Hospital	96	Hospital—unhealthy	97	2	5	1
				United States							
25	Seattle, WA	1985–1995	18–65	Oral cavity, pharynx	Cancer registry	54, 63 <sup>d</sup>	Random digit dialing	63, 61 <sup>d</sup>	2	1	1
26	Iowa	1993–2006	>17	Oral cavity, pharynx, larynx	Hospital	87	Hospital—healthy	92	6	1	0
27	North Carolina	1994–1997	>17	Oral cavity, pharynx, larynx	Hospital	88	Hospital—unhealthy	86	4	2	0
28	Tampa, FL	1999–2003	≥18	Oral cavity, pharynx, larynx	Hospital	98	Cancer-screening clinic (healthy)	90	1	1	1
29	Los Angeles, CA	1999–2004	18–65	Oral cavity, pharynx, larynx	Cancer registry	49	Neighborhood	68	2	1	1
30	Houston, TX	2001–2006	N/R	Oral cavity, pharynx, larynx	Hospital	95	Hospital visitors	>80	4	1	0
				Latin America							
31	Puerto Rico	1992–1995	21–79	Oral cavity, pharynx	Cancer registry	71	Residential records	83	9	5	0
	Latin America <sup>e</sup>	2000–2003	15–79	Oral cavity, pharynx, larynx	Hospital	95	Hospital—unhealthy	86	7	0	0
				Cross-regional <sup>f</sup>							
32	Italy, Spain, Ireland, Poland, Canada, Australia, Cuba, India, Sudan	1992–1997	N/R	Oral cavity, pharynx	Hospital	89	Hospital/community	87	1	1	3

Abbreviations: INHANCE, International Head and Neck Cancer Epidemiology; N/R, no age restriction.

<sup>a</sup> Representative publication in which the study methods are available.<sup>b</sup> All studies frequency matched controls to cases minimally on age and sex. Additional frequency matching factors included center (Italy, Central Europe, Latin America, and International Multicenter studies), hospital (France study), ethnicity (Tampa and Los Angeles studies), and neighborhood (Los Angeles study).<sup>c</sup> The participation rate was not formally assessed; the estimated response rate is reported.<sup>d</sup> Two response rates are reported because data were collected in 2 population-based case-control studies, the first from 1985 to 1989 among men and the second from 1990 to 1995 among men and women.<sup>e</sup> Study centers: Buenos Aires, Havana, Goiânia, Pelotas, Porto Alegre, Rio de Janeiro, and São Paulo.<sup>f</sup> Multicenter study. Study centers in India (Madras, Trivandrum, and Bangalore) and Sudan were excluded from analysis because of the very low prevalence of alcohol consumption.



**Figure 1.** Study-specific head and neck cancer odds ratios for consumption of separate alcoholic beverages—pure drinkers versus never drinkers. Diamond symbols represent odds ratios; symbol size is proportional to the number of cases among never drinkers and pure drinkers of that beverage. Horizontal lines represent 95% confidence intervals. The P value for the test of heterogeneity across individual studies is shown at the bottom of each graph. OR, odds ratio; Int., International.

among all study subjects (i.e., including drinkers of multiple beverage types).

We used a 2-stage random effects modeling approach (33) for our pooled analysis of alcoholic beverage types. At the first stage, associations between HNC and measures of alcoholic beverage consumption were assessed by estimating odds ratios and 95% confidence intervals based on unconditional logistic regression models for each case-control study. To adjust for matching factors and potential confounding, we included age (categories shown in Web Table 2), sex, education, race/ethnicity, study center, pack-years of cigarette smoking, years of cigar smoking (continuous), and years of pipe smoking (continuous) in all models. Analyses conducted among all study subjects (i.e., including drinkers of multiple beverage types) were also adjusted for consumption frequency of other beverages. For subjects missing information on educational level (535 cases, 438 controls), we applied multiple imputation using the PROC MI procedure (SAS, version 9, software; SAS Institute, Inc., Cary, North Carolina) under the assumption that the education data were missing at random (34). Within each geographic region, we predicted educational level using logistic regression models with parameters for age, sex, race/ethnicity,

study, and case/control status (35). The logistic regression results to assess summary estimates for alcoholic beverage consumption for the 5 imputations were combined by using the PROC MIANALYZE procedure (SAS Institute, Inc.).

At the second stage of analysis, summary effect estimates were calculated by using a maximum-likelihood-based random effects model. We tested for evidence of heterogeneity between the study-specific odds ratios for categories of alcoholic beverage use by calculating likelihood ratio tests comparing the deviance statistics from main-effects models with those from models specifying interaction between alcoholic beverage consumption and study.

Among pure drinkers, we conducted a test of heterogeneity in odds ratio estimates for levels of ethanol-standardized consumption frequency across the 3 beverage types. This was performed by constructing a likelihood ratio test comparing the deviance statistic of a model containing beverage-specific parameters for consumption frequency with that of a constrained model with parameters for different levels of consumption frequency specified as being identical across beverage types.

We also conducted additional analyses stratifying by geographic region (Europe, North America, Latin America),

**Table 2.** Head and Neck Cancer Risk and Pure Consumption of Beer, Wine, and Liquor, With Never Drinkers as the Referent Group, in the INHANCE Consortium

	Beer-only Drinkers + Never Drinkers			Liquor-only Drinkers + Never Drinkers			Wine-only Drinkers + Never Drinkers		
	No. of Cases	No. of Controls	Odds Ratio <sup>a</sup> (95% CI)	No. of Cases	No. of Controls	Odds Ratio (95% CI)	No. of Cases	No. of Controls	Odds Ratio (95% CI)
Never drinker	1,124	3,487	1.0	1,124	3,487	1.0	1,124	3,487	1.0
No. of ethanol- standardized drinks per week									
≤5	215	414	1.6 (1.3, 2.1)	161	276	1.6 (1.0, 2.6)	128	477	1.1 (0.8, 1.6)
6–15	228	304	1.9 (1.4, 2.7)	116	121	1.5 (1.0, 2.4)	157	722	1.2 (0.8, 1.9)
16–30	136	146	2.2 (1.3, 3.5)	97	70	2.3 (1.4, 4.0)	209	733	1.9 (0.9, 3.9)
>30	279	122	5.4 (3.1, 9.2)	125	60	3.6 (2.2, 5.8)	527	527	6.3 (2.2, 18.6)
<i>P</i> <sub>trend</sub>			<0.0001			<0.0001			<0.0001
<i>P</i> <sub>heterogeneity</sub> <sup>b</sup>			0.002			0.02			<0.0001
Years of consumption									
≤10	82	134	1.8 (1.2, 2.6)	37	70	1.5 (0.8, 2.7)	40	131	1.5 (0.9, 2.5)
11–20	80	159	1.5 (1.0, 2.1)	42	66	1.5 (0.8, 2.6)	46	183	1.6 (0.8, 3.2)
21–40	462	496	2.5 (1.7, 3.6)	233	255	2.1 (1.3, 3.5)	519	1,237	1.9 (1.2, 3.0)
>40	225	189	2.2 (1.6, 3.0)	184	134	2.6 (1.6, 4.3)	410	898	1.7 (0.9, 3.2)
<i>P</i> <sub>trend</sub>			0.40			0.24			0.46
<i>P</i> <sub>heterogeneity</sub>			0.005			0.002			<0.0001
Cumulative consumption, drink-years									
≤10	177	335	1.8 (1.4, 2.3)	103	219	1.3 (0.8, 1.9)	75	367	1.0 (0.7, 1.4)
11–20	77	145	1.6 (1.1, 2.4)	62	94	1.5 (0.8, 2.6)	50	162	1.6 (1.0, 2.8)
21–40	115	168	2.1 (1.5, 3.0)	73	75	1.7 (1.0, 2.8)	65	313	1.1 (0.7, 1.8)
41–80	132	152	1.9 (1.3, 2.7)	88	51	3.6 (1.9, 6.9)	118	529	1.4 (0.7, 2.9)
>80	348	178	4.0 (2.5, 6.6)	170	86	2.9 (1.8, 4.7)	707	1,078	4.0 (1.8, 9.0)
<i>P</i> <sub>trend</sub>			0.005			0.21			<0.0001
<i>P</i> <sub>heterogeneity</sub>			0.0006			0.03			<0.0001

Abbreviations: CI, confidence interval; INHANCE, International Head and Neck Cancer Epidemiology.

<sup>a</sup> Odds ratios adjusted for age, sex, race/ethnicity, study center, educational level, pack-years of smoking, years of cigar smoking, and years of pipe smoking.

<sup>b</sup> *P* value for the test of odds ratio heterogeneity across studies.

study design (hospital based, population based), cancer site (oral, pharynx, larynx), smoking history (never smoked, ever smoked), sex, and age (<55, ≥55 years). We also conducted influence analyses, where each study was excluded one at a time to assess the impact upon the magnitude of the overall summary estimate and its statistical significance.

All reported *P* values are 2 sided.

## RESULTS

Of the 9,107 cases and 14,219 controls included in the analysis, approximately 88% and 75%, respectively, reported alcohol consumption. The majority of drinkers reported consuming multiple beverage types (70% of case drinkers, 63% of control drinkers). Among pure drinkers, the most common beverage reported was wine (43% of case pure drinkers, 62%

of control pure drinkers), followed by beer (36% of case pure drinkers, 25% of control pure drinkers) and liquor (21% of case pure drinkers, 13% of control pure drinkers). Selected characteristics of cases and controls are shown in Web Table 2. As expected, the distribution of pure beverage consumption differed substantially by geographic region; the majority of wine-only drinkers were European (83% of cases, 87% of controls), and most beer-only drinkers were North American (71% of cases, 53% of controls). Pure liquor consumption varied by geographic region to a lesser extent than for beer and wine; a plurality of liquor-only drinkers were from North America (45% of cases, 46% of controls). Pure drinkers and multiple-beverage drinkers were similar in their distributions by age, sex, ethnicity, educational level, and pack-years of cigarette use. Women and never smokers were less likely to consume alcohol.

**Table 3.** Head and Neck Cancer Risk and Pure Ethanol-standardized Consumption of Beer, With Analysis Stratified by Selected Study and Subject Characteristics, in the INHANCE Consortium

	No. of Standardized Drinks per Week								<i>P</i> <sub>heterogeneity</sub> <sup>a</sup>
	Never Drinker (Reference Group)		Beer-only Drinker						
			≤15			>15			
			No. of Cases	No. of Controls	Odds Ratio <sup>b</sup> (95% CI)	No. of Cases	No. of Controls	Odds Ratio (95% CI)	
Region									
North America	537	1,477	296	383	2.0 (1.5, 2.6)	316	144	4.1 (2.2, 7.6)	0.45
Latin America	305	712	104	216	1.5 (0.7, 3.2)	67	89	2.1 (0.8, 5.7)	0.15
Europe	277	1,285	42	117	1.4 (0.6, 3.2)	32	35	3.5 (1.2, 10.4)	0.10
Study design									
Hospital based	1,007	3,080	377	566	1.8 (1.4, 2.2)	360	221	3.4 (2.1, 5.6)	<0.01
Population based	117	407	66	152	1.7 (0.6, 4.7)	55	47	3.1 (0.7, 13.1)	0.01
Cancer site <sup>c</sup>									
Oral cavity	344	3,487	108	718	2.0 (1.4, 2.8)	120	268	6.4 (3.9, 10.3)	0.15
Pharynx	330	3,487	167	718	2.3 (1.7, 3.1)	151	268	4.3 (2.7, 6.8)	0.42
Larynx	285	3,487	116	718	1.6 (1.1, 2.2)	97	268	2.7 (1.7, 4.4)	0.29
Ever smoked cigarettes									
No	480	2,124	77	271	1.2 (0.8, 1.8)	22	46	1.9 (0.9, 4.1)	0.40
Yes	644	1,360	366	447	2.3 (1.8, 3.0)	393	221	4.1 (2.5, 6.7)	<0.01
Sex									
Males	513	1,698	329	578	1.7 (1.3, 2.2)	366	249	3.6 (2.4, 5.4)	0.23
Females	611	1,789	114	140	2.1 (1.4, 3.1)	49	19	2.1 (0.3, 13.5)	<0.01
Age, years									
<55	381	1,448	192	376	1.9 (1.4, 2.7)	170	137	3.6 (2.1, 6.0)	0.31
≥55	743	2,039	251	342	1.7 (1.3, 2.2)	245	131	3.5 (2.3, 5.2)	0.03

Abbreviations: CI, confidence interval; INHANCE, International Head and Neck Cancer Epidemiology.

<sup>a</sup> *P* value for test of odds ratio heterogeneity across studies.<sup>b</sup> Odds ratios adjusted for age, sex, race/ethnicity, study center, educational level, pack-years of smoking, years of cigar smoking, and years of pipe smoking.<sup>c</sup> Excludes 415 cancers without site information, of overlapping head and neck sites, or of oral cavity/pharynx, not otherwise specified.

### Analyses of pure drinkers of each beverage type

Figure 1 shows study-specific odds ratios for beer, liquor, and wine consumption (vs. alcohol never drinkers) from analyses restricted to alcohol never drinkers and pure drinkers. The study-specific odds ratios were fairly homogeneous for beer but not for liquor or wine; tests of between-study heterogeneity for the latter 2 beverage types were statistically significant. In particular, the heterogeneity for wine consumption was greatest among the European studies. The random effects summary odds ratios for ever drinking of beer, liquor, and wine were 2.1 (95% confidence interval (CI): 1.6, 2.7), 2.2 (95% CI: 1.4, 3.4), and 1.6 (95% CI: 1.0, 2.6), respectively.

The results from pooled analyses of ethanol-standardized beverage consumption frequency and duration among pure drinkers of each beverage type are summarized in Table 2. All summary odds ratio estimates demonstrated between-study heterogeneity. We observed similar associations with HNC risk among beer-only drinkers (odds ratios (ORs) = 1.6, 1.9, 2.2, and 5.4 for ≤5, 6–15, 16–30, and >30 drinks

per week, respectively) and liquor-only drinkers (ORs = 1.6, 1.5, 2.3, and 3.6) relative to never drinkers. Associations with years of consumption and lifetime cumulative consumption were also comparable between beer-only and liquor-only drinkers. Among wine-only drinkers, odds ratios for moderate levels of consumption were close to null (ORs = 1.1 and 1.2 for ≤5 and 6–15 drinks per week, respectively); increases in risk were observed only for higher consumption levels (ORs = 1.9 and 6.3 for 16–30 and >30 drinks per week, respectively). A test of heterogeneity in odds ratio estimates for levels of consumption frequency across all 3 beverage types was statistically significant (*P* < 0.01). When we conducted pairwise tests of heterogeneity between beverage types, it became apparent that the odds ratio estimates for wine-only drinkers were the source of the heterogeneity (beer vs. liquor, *P* = 0.60; beer vs. wine, *P* < 0.01; liquor vs. wine, *P* = 0.02).

Study-specific results (Web Tables 3–5) were inspected, and influence analyses were performed to attempt to identify sources of between-study heterogeneity in the pooled estimates of ethanol-standardized beverage consumption

**Table 4.** Head and Neck Cancer Risk and Pure Ethanol-standardized Consumption of Liquor, With Analysis Stratified by Selected Study and Subject Characteristics, in the INHANCE Consortium

	No. of Standardized Drinks per Week								<i>P</i> <sub>heterogeneity</sub> <sup>a</sup>
	Never Drinker (Reference Group)		Liquor-only Drinker						
			≤15			>15			
No. of Cases	No. of Controls	No. of Cases	No. of Controls	Odds Ratio <sup>b</sup> (95% CI)	No. of Cases	No. of Controls	Odds Ratio (95% CI)		
Region									
North America	537	1,477	101	172	1.9 (0.8, 4.4)	123	69	3.2 (1.5, 6.6)	0.01
Latin America	305	712	34	25	2.1 (0.4, 9.6)	65	38	2.6 (0.6, 11.1)	0.97
Europe	277	1,285	142	199	1.2 (0.6, 2.5)	32	20	1.7 (0.4, 6.9)	0.02
Study design									
Hospital based	1,007	3,080	241	317	1.6 (1.1, 2.2)	175	101	3.0 (2.0, 4.7)	0.01
Population based	117	407	36	80	2.3 (0.1, 43.6)	47	29	1.8 (0.1, 25.8)	0.02
Cancer site <sup>c</sup>									
Oral cavity	344	3,487	80	397	1.7 (0.9, 3.3)	53	130	3.2 (1.6, 6.4)	0.11
Pharynx	330	3,487	65	397	2.0 (0.9, 4.6)	86	130	3.6 (2.0, 6.3)	<0.01
Larynx	285	3,487	108	397	1.6 (0.8, 3.1)	58	130	1.9 (0.9, 3.9)	0.06
Ever smoked cigarettes									
No	480	2,124	30	123	1.2 (0.5, 2.9)	5	22	3.5 (0.5, 25.6)	0.20
Yes	644	1,360	247	273	1.8 (1.1, 3.0)	217	108	3.3 (1.8, 6.1)	<0.01
Sex									
Males	513	1,698	188	274	1.8 (1.2, 2.8)	181	110	3.0 (1.8, 5.7)	<0.01
Females	611	1,789	89	123	1.1 (0.6, 2.0)	41	20	2.2 (0.9, 5.2)	0.13
Age, years									
<55	381	1,448	75	137	1.0 (0.3, 2.7)	49	36	2.7 (1.0, 7.1)	<0.01
≥55	743	2,039	202	260	1.8 (1.2, 2.6)	173	94	3.0 (2.0, 4.7)	0.20

Abbreviations: CI, confidence interval; INHANCE, International Head and Neck Cancer Epidemiology.

<sup>a</sup> *P* value for test of odds ratio heterogeneity across studies.

<sup>b</sup> Odds ratios adjusted for age, sex, race/ethnicity, study center, educational level, pack-years of smoking, years of cigar smoking, and years of pipe smoking.

<sup>c</sup> Excludes 415 cancers without site information, of overlapping head and neck sites, or of oral cavity/pharynx, not otherwise specified.

frequency among pure drinkers and never drinkers. The summary odds ratios for beer-only consumption were influenced slightly by exclusion of the Iowa study (OR = 1.6, 1.7, 1.7, and 4.2 for ≤5, 6–15, 16–30, and >30 drinks per week, respectively), although statistically significant between-study heterogeneity remained (*P* < 0.0001). Exclusion of the Tampa study influenced the pooled results for consumption of liquor only (ORs = 1.5, 1.8, 1.9, and 3.2); no residual between-study heterogeneity was detected (*P* = 0.15). The associations with pure wine consumption became considerably weaker in magnitude upon exclusion of the Switzerland study (ORs = 1.0, 1.0, 1.4, and 3.7) and increased with exclusion of the Milan study (ORs = 1.2, 1.4, 2.4, and 8.7); in each case, however, substantial heterogeneity was still present among the remaining pooled studies.

The results of stratified analyses of pure ethanol-standardized beverage consumption level (never drinker, ≤15, >15 drinks per week) are summarized in Tables 3–5. We observed some differences between geographic regions in the magnitude of risk for the highest consumption level. For beer,

summary odds ratio estimates for North American studies (ORs = 2.0 and 4.1 for ≤15 and >15 standard drinks per week, respectively) were slightly stronger than those for studies from Europe (ORs = 1.4 and 3.5) and Latin America (ORs = 1.5 and 2.1). For liquor, the summary odds ratio estimates for North American studies (ORs = 1.9 and 3.2) and Latin American studies (ORs = 2.1 and 2.6) were stronger than those of studies from Europe (ORs = 1.2 and 1.7). For wine, the odds ratio estimates for European studies (ORs = 1.5 and 4.0) were stronger than those for studies from North America (ORs = 1.1 and 2.8) and Latin America (ORs = 1.1 and 3.7). Odds ratios were stronger for oral and pharyngeal cancer than for laryngeal cancer and among smokers compared with never smokers. The pattern of associations across beverage types did not change with anatomic site or smoking status. Additional analyses investigating the joint effects of smoking and pure beverage consumption (ever vs. never drinker) also did not meaningfully differ by beverage type (results not shown). Beverage associations did not differ by study design, sex, or age group.

**Table 5.** Head and Neck Cancer Risk and Pure Ethanol-standardized Consumption of Wine, With Analysis Stratified by Selected Study and Subject Characteristics, in the INHANCE Consortium

	No. of Standardized Drinks per Week								<i>P</i> <sub>heterogeneity</sub> <sup>a</sup>
	Never Drinker (Reference Group)		Wine-only Drinker						
			≤15			>15			
			No. of Cases	No. of Controls	No. of Cases	No. of Controls	Odds Ratio <sup>b</sup> (95% CI)	No. of Cases	
Region									
North America	537	1,477	70	236	1.1 (0.7, 1.8)	12	9	2.8 (0.5, 15.5)	0.17
Latin America	305	712	39	52	1.1 (0.6, 1.9)	50	15	3.7 (1.7, 7.8)	0.03
Europe	277	1,285	173	907	1.5 (0.6, 3.4)	673	1,233	4.0 (1.4, 11.2)	<0.01
Study design									
Hospital based	1,007	3,080	267	1,121	1.2 (0.8, 1.9)	734	1,257	3.6 (1.8, 7.3)	<0.01
Population based	117	407	18	78	1.2 (0.3, 5.1)	2	3		0.19
Cancer site <sup>c</sup>									
Oral cavity	344	3,487	83	1,199	1.3 (0.7, 2.2)	133	1,260	5.9 (2.3, 15.4)	<0.01
Pharynx	330	3,487	77	1,199	1.4 (0.9, 2.2)	231	1,260	4.4 (2.0, 9.6)	<0.01
Larynx	285	3,487	97	1,199	1.2 (0.6, 2.3)	298	1,260	3.9 (1.2, 13.0)	<0.01
Ever smoked cigarettes									
No	480	2,124	84	630	1.3 (0.8, 2.0)	38	420	1.6 (0.8, 3.1)	<0.01
Yes	644	1,360	201	569	1.2 (0.7, 2.2)	698	840	3.7 (1.5, 9.1)	<0.01
Sex									
Males	513	1,698	155	615	1.1 (0.7, 1.9)	655	1,051	3.6 (1.4, 8.8)	<0.01
Females	611	1,789	130	584	1.2 (0.7, 1.9)	81	209	3.6 (1.9, 6.8)	<0.01
Age, years									
<55	381	1,448	93	405	1.5 (1.0, 2.2)	198	430	2.8 (1.3, 5.8)	0.09
≥55	743	2,039	192	794	1.2 (0.7, 2.0)	538	830	3.6 (1.4, 8.9)	<0.01

Abbreviations: CI, confidence interval; INHANCE, International Head and Neck Cancer Epidemiology.

<sup>a</sup> *P* value for test of odds ratio heterogeneity across studies.<sup>b</sup> Odds ratios adjusted for age, sex, race/ethnicity, study center, educational level, pack-years of smoking, years of cigar smoking, and years of pipe smoking.<sup>c</sup> Excludes 415 cancers without site information, of overlapping head and neck sites, or of oral cavity/pharynx, not otherwise specified.

## Analyses of all study subjects

In our pooled analysis of all study subjects, the pattern of findings across alcoholic beverage types was comparable to that observed in the analysis of pure drinkers (Web Table 6).

## DISCUSSION

Overall, we found estimates of the relative risks of HNC associated with alcohol consumption to be very similar for beer and liquor. In light of our use of ethanol-standardized estimates of beverage consumption frequency, our finding of similar associations with risk for beer and liquor consumption argues in favor of ethanol and its metabolites as the principal carcinogenic agents in these alcoholic beverages, rather than beverage-specific constituents. We cannot rule out the possibility that another byproduct of alcohol production—created at levels highly correlated with ethanol concentration—is in fact the actual HNC carcinogen in

alcoholic beverages. To our knowledge, no such candidate compound has been identified.

Our summary odds ratio estimates for wine consumption, however, were somewhat different from those for the other 2 beverage types. Whereas the dose-response relation was generally linear for beer and liquor, no such trend was observed for wine. At moderate levels of consumption, the odds ratio estimates for wine were much weaker than the corresponding estimates for beer or liquor. At a high consumption level (>30 standard drinks per week), the odds ratio estimate for wine was generally comparable to those of the other beverage types. This pattern in risk across beverage types was consistent across most subgroup strata with nonsparse numbers, and it was also apparent in analyses of all subjects (i.e., pure and mixed-beverage drinkers), suggesting that these findings are not attributable to issues concerning the study of pure drinkers.

One possible reason for the observed weaker association with moderate wine consumption is that it reflects residual confounding. Wine consumption has been associated with



higher intake of a healthy diet, higher education, and lower smoking levels in studies conducted in the United States and Northern Europe (36–38). Although we performed detailed adjustment for education and smoking in our modeling, we did not adjust for diet or other lifestyle factors that may influence the risk of HNC, and we may not have completely accounted for the effects of smoking. Had we been able to do so, the associations among wine drinkers may have been more similar to those among beer and liquor drinkers. A second possible explanation involves the fact that wine is more frequently consumed during meals than other alcoholic beverages (39). The possibility of an “alcohol washing effect” by the chewing and swallowing of foods has been proposed, whereby ingestion of foods could “wash” alcohol drinking and reduce the effect of ethanol and its carcinogenic metabolites on the oral, pharyngeal, and esophageal mucosa (40, 41). Finally, it is possible that the carcinogenic effects of ethanol in these beverages are offset by other anticarcinogenic compounds in wine such as resveratrol, a phenolic compound with antioxidant properties present in red wine that has been shown to inhibit tumor initiation and progression in experimental studies (4). We did not have information on the type of wine consumed (red vs. white) for our pooled analysis; consequently, we could not investigate this hypothesis further. We caution that this last explanation is speculative, given the paucity of supporting evidence.

Some differences between regions in associations with beer (strongest in North America), liquor (strongest in North and Latin America), and wine (strongest in Europe) were observed in the analysis of pure drinkers. This may reflect differences within each broad category of beverage consumption level used in the subgroup analyses ( $<15$ ,  $\geq 15$  standard drinks per week) in the average number of drinks per week from each region, given that the consumption levels of beer, liquor, and wine were highest among studies from North America, North and Latin America, and Europe, respectively. Another possible explanation is that these differences may indicate greater accuracy in assessing lifetime consumption patterns (and thus less attenuation of the effect due to misclassification) for the beverage predominant in that region (42).

We did not observe any clear differences between beverage types in analyses stratified by smoking status. However, the odds ratio estimates for each beverage type were stronger and more stable among smokers compared with those among never smokers. These differences are consistent with effect modification between alcohol and tobacco use, evidence of which has been previously reported by several studies (43). It is biologically plausible that alcohol consumption could amplify the carcinogenic effects of smoking, as ethanol has been shown to increase the permeability of oral mucosa to tobacco combustion products (44, 45).

We also did not observe meaningful differences across beverage types with regard to their associations with HNC at different anatomic sites. However, the odds ratio estimates for alcohol consumption were stronger for cancers of the oral cavity and pharynx than for laryngeal cancers, irrespective of beverage type. This pattern has been previously reported in several studies and is biologically plausi-

ble given that the oral cavity and pharynx are directly exposed to alcoholic beverages, whereas only parts of the larynx (supraglottis and epilarynx) are exposed.

An important strength of our study is its large size. The INHANCE Consortium, with detailed information on lifetime alcohol consumption for more than 9,000 cases and 14,000 controls from 15 case-control studies, is a unique resource for investigating whether beer, liquor, and wine consumptions are differentially associated with HNC risk. In particular, the large size of this study enabled us to estimate associations with alcohol consumption among individuals who reported consuming only beer, wine, or liquor. As such, it is, by far, the largest study to investigate beverage effects among pure drinkers. Comparisons across pure-drinker subgroups arguably represent the most informative means of investigating whether the relative risk of HNC from alcohol consumption differs by alcoholic beverage type.

This study also has limitations. Foremost among these is the presence of heterogeneity in study-specific results for each measure of alcohol consumption examined, which limits the conclusions that can be made from our pooled analysis. Our inspection of study-specific findings, influence analyses, and subgroup analyses stratifying by study characteristics did not generally point to any clear sources of heterogeneity, although exclusion of the Tampa study from the pooled analysis of ethanol-adjusted frequency of liquor-only consumption resulted in a heterogeneity test statistic that was no longer statistically significant. Differences across studies in the wording and design of their questions assessing lifetime alcohol consumption are a potential source of heterogeneity. A second study limitation, which may contribute to the observed heterogeneity, is the absence of more detailed information regarding alcoholic beverages (e.g., red vs. white wine consumption, beverage-specific percentage of ethanol content for a given country, the use of nonalcoholic “mixers” with liquor). Such unmeasured differences among the underlying study populations in their alcoholic beverage consumption patterns could contribute to between-study heterogeneity. For example, the heterogeneity for liquor consumption may be due, in part, to possible differences among study populations in the type of liquor consumed and/or the frequency with which liquor is consumed “straight” versus “mixed.” There is some evidence that ethanol concentration, independent of ethanol amount, may influence HNC risk (16). A third limitation is our inability to adjust for dietary factors or other lifestyle characteristics that could potentially confound our findings. Finally, we acknowledge the inherent limitation of the retrospective case-control design for investigating the etiologic relevance of past exposures such as lifetime alcohol consumption.

In conclusion, we observed comparable estimates of HNC relative risk for consumption of beer, liquor and, at high consumption levels, wine in our pooled analysis within the INHANCE Consortium. We observed, however, a comparatively weaker risk at low consumption levels for wine than for the other beverage types. Given the presence of heterogeneity in study-specific results and the possible existence of confounding from diet and other lifestyle factors, our findings should be interpreted with caution.

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## APPENDIX

The definitions of ever alcohol drinking were as follows: “ever” consumed alcohol (Central Europe; Aviano, Milan, and Italy Multicenter; France; and Switzerland studies); >4 drinks in a year (Seattle study); ≥1 drink per month for ≥6 months in a lifetime (Los Angeles study); ≥12 drinks of a kind of alcohol in a lifetime (Puerto Rico study); once or more per month (Multicenter, Latin America studies); average ≥1 drink per week for ≥1 year (Iowa study), once or more per week for ≥1 year (Tampa and Houston studies); ≥4 times per month of beer, wine, or liquor (North Carolina study).